Prevention of bladder cancer incidence and recurrence: nutrition and lifestyle

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Abstract: PURPOSE OF REVIEW: We review the influence of nutrition and lifestyle on bladder cancer incidence and recurrence and summarize food items, diets and lifestyle practices that physicians may wish to prioritize for discussion with their patients. RECENT FINDINGS: Recent study results suggest an association between bladder cancer incidence and several food items including meat, fruit, vegetables, milk products and oil. Micronutrient deficiency is associated with bladder cancer risk; however, it remains unclear if micronutrient supplementation can modify bladder cancer incidence. Furthermore, total fluid intake, alcohol, coffee and tea seem to have no influence on bladder cancer incidence. There is weak evidence that stress, anxiety and lack of sleep may increase the risk of developing bladder cancer, whereas exercise may reduce the risk of dying from it. SUMMARY: Several dietary items and life styles are associated with bladder cancer incidence and recurrence. However, besides smoking cessation, there is no evidence that a certain diet or lifestyle can decrease bladder cancer incidence.

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Prevention of bladder cancer incidence and recurrence: nutrition and lifestyle

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We review the influence of nutrition and lifestyle on bladder cancer incidence and recurrence and summarize food items, diets and lifestyle practices that physicians may wish to prioritize for discussion with their patients.

Recent findings
Recent study results suggest an association between bladder cancer incidence and several food items including meat, fruit, vegetables, milk products and oil. Micronutrient deficiency is associated with bladder cancer risk; however, it remains unclear if micronutrient supplementation can modify bladder cancer incidence. Furthermore, total fluid intake, alcohol, coffee and tea seem to have no influence on bladder cancer incidence. There is weak evidence that stress, anxiety and lack of sleep may increase the risk of developing bladder cancer, whereas exercise may reduce the risk of dying from it.

Summary
Several dietary items and life styles are associated with bladder cancer incidence and recurrence. However, besides smoking cessation, there is no evidence that a certain diet or lifestyle can decrease bladder cancer incidence.

Keywords
bladder cancer, diet, dietary supplements, lifestyle, physical activity, prevention

INTRODUCTION

Bladder cancer is the second most common malignancy of the urinary tract, with an estimated 429 793 new diagnoses and 165 084 bladder cancer deaths per year worldwide [1]. An increase by 41% from currently 124 188 up to 174 891 new cases per year is expected in the European Union by the year 2035 [1]. Because of costly lifetime surveillance with periodic cystoscopy and relevant recurrence rates, bladder cancer has the highest lifetime treatment costs per patient of all cancers ranging from $100 000 to $200 000 [2]. This significant financial burden on the population and healthcare system calls for effective bladder cancer prevention and control.

In this report, we briefly review the influence of nutrition and lifestyle on bladder cancer incidence and recurrence. We summarize food items, diets and lifestyle practices that physicians may wish to recommend to their patients. For the purpose of this review, we will not discuss smoking which is covered elsewhere in this issue, although this represents the most important risk factor for bladder cancer [3].

METHODS

We conducted a literature search on 7 August 2017 using the Medline database. For our literature research, we used combinations, synonyms and related search terms to 'bladder' and 'cancer' and 'nutrition' or 'lifestyle' and selected the time period between 1st of January 2016 until 7th of August 2017. The following search terms were used: (((Nutrit*[Title/Abstract] OR vitamin[Title/Abstract] OR food[Title/Abstract] OR diet[Title/Abstract] OR intake[Title/Abstract] OR consumption[Title/Abstract] OR alcohol[Title/Abstract] OR lifestyle[Title/Abstract])) AND ((uroth*[Title/Abstract] OR bladder [Title/Abstract]) AND ((cancer[Title/Abstract] OR

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KEY POINTS

- A diet rich of vegetables and fruits might be protective against bladder cancer.
- Exercise seems to play a beneficial role in reducing the risk of death from bladder cancer.
- There are weak associations between stress, anxiety and lack of sleep and the risk of developing bladder cancer.
- Coffee, tea and moderate alcohol intake does not seem to be a risk factor for bladder cancer.
- There is no evidence that any specific micronutrient supplement is reducing the incidence or recurrence risk of bladder cancer.
- The abundance of drinking water byproducts is worrisome.
- Given the increasing incidence and high costs of bladder cancer, more prospective cohort studies with prespecified statistical analyses are mandatory.

carcinoma[Title/Abstract] OR neoplasm[Title/Abstract] OR neoplasms[Title/Abstract] OR tumor[Title/Abstract] OR tumors [Title/Abstract] OR tumour [Title/Abstract] OR tumours[Title/Abstract]))))). Non-English literature, animal studies, case reports, studies observing the influence of medication, enhanced recovery after surgery studies and correspondence/letters were excluded.

NUTRITION

Diet

Statistical analyses of food questionnaires remain challenging, especially when many food items are collected. To facilitate the analysis, several items are summarized into 'dietary scores'. Although a recent cohort study summarizing a questionnaire including 121 food-items into different dietary-scores found no significant association [4], a case–control study summarizing an 80 food-item questionnaire into an 'inflammatory diet score' reported a positive association with bladder cancer [5]. Regarding single food items, the comprehensive review and meta-analysis by Al-Zalabani described associations between bladder cancer and intakes of processed meat, fruit, vegetables, citrus fruit and cruciferous vegetables [6▪▪]. In addition, a narrative review by Piyathilake [7] discussed potential associations with bladder cancer and sour milk, yogurt and olive oil.

Coffee and alcohol

In the past, coffee has been regarded as a potential carcinogen because of a reported association between increased coffee intake and higher bladder cancer risk. However, several new studies including a recent case–control study revealed that residual confounding factors, especially smoking status which is correlated with coffee consumption, may have been responsible for this association [8,9]. Indeed, a pooled analysis of two Japanese cohort studies reported a protective effect of increased coffee consumption [10]. However, given that in this study only 274 cancer cases were observed, this multivariable analysis included a high number of 15 variables. For tea consumption, a recent meta-analysis including 25 case–control studies, 15 634 cases and 30 975 controls found no association with bladder cancer [11].

Ethanol is a known risk factor for several malignancies and three recent studies focused on associations of bladder cancer incidence and alcohol consumption. A large European cohort study observed 476 160 individuals for 13.9 years on average and reported no significant association between baseline alcohol intake and bladder cancer [12]. Again, no prior statistical analysis plan was defined and in subsequent univariate analyses of several strata (alcohol intake or spirit intake in quartiles and binary smoking status), several significant associations emerged. A recent study from Masaoka *et al.* [13] discussed a potential effect modification of aldehyde dehydrogenase polymorphism and varying production of acetaldehyde, which is regarded as a main carcinogen byproduct of ethanol. Finally, a case–control study by Zaitsu *et al.* [14] using a Japanese inpatient database found a higher risk of bladder cancer in heavy drinkers [odds ratio (OR) 1.33, 95% confidence interval (CI) 1.06–1.66]. The authors speculate that the Japanese population may have a weak genetic tolerance to acetaldehyde.

Micronutrients

Several studies have looked at micronutrient deficiency as potential risk factors and micronutrient supplementation as potential preventive intervention, respectively. For vitamin D, the evidence has just recently been summarized in a narrative review [15], in a systematic review [16] and in a meta-analysis [17] demonstrating that patients with low vitamin D levels are associated with an increased risk of developing bladder cancer. This is supported by the results of a case–control study from Tunisia describing an increased risk of bladder cancer in patients with vitamin D deficiency [18]. However,

in contrast to these findings, a study from Taiwan observed an increased risk of bladder cancer in patients taking vitamin D (OR 4.97, 95% CI 4.40–5.60) [19] The authors speculate that this cohort of patients were also taking high doses of oral calcium and phosphate as well and this may have down regulated the active form of vitamin D3 in the patients' body and this in turn increased the risk of bladder cancer. Further systematic reviews described an association of higher vitamin A, D, E and selenium levels and/or vitamin supplement intake and a lower risk of bladder cancer [20]. It may be noteworthy that vitamin levels or supplement intake is associated with a certain life style, BMI, physical activity, smoking status, diet and access to healthcare which all represent potential confounders. So far, interventional trials have failed to confirm a protective effect of micronutrients against bladder cancer [21].

Fluid intake

Because of the impact on voiding volume and frequency, total fluid intake and certain beverages have been evaluated but lead to contradictory results. Some authors argue that a lower amount of fluid intake may be associated with a higher incidence of bladder cancer because a lower urinary output would increase the concentration of carcinogens in the urine and their contact time with the urothelial surface. In contrast, it has been hypothesized that an increasing intake of fluids and subsequent urine output may lead to bladder distention and deep layer penetration of carcinogens and that an increasing intake of water or beverages containing carcinogenic components may lead to an increased incidence of bladder cancer. Furthermore, certain medications (e.g. ranitidine [22]) may lead to an increased urinary excretion of specific carcinogens.

Just recently, a new case–control study, a systematic review and meta-analysis looking at water intake and bladder cancer risk have been published. In this Italian case–control study, total water from beverages, water from bottled water, alcoholic beverages, milk, fruit juice and soft drinks or total water from any foods or specific foods was not significantly associated with bladder cancer risk. After multiple testing, only an association between an increased intake of water from vegetables and a lower incidence of bladder cancer was observed [23]. The systematic review and meta-analysis from Liu *et al*. [24] summarized the results of 21 case–control and five cohort studies regarding the association of total fluid intake and bladder cancer risk. This review did not adhere to PRISMA guidelines and showed several limitations including a limited search protocol and no a priori variable or subgroups selection. Although total fluid intake was not associated with the risk of bladder cancer, the authors reported a significant association of higher fluid intake and a higher incidence of bladder cancer in the following subgroups: in the group including all men, in European men but not in American men and a weak association in American residents. In contrast, a protective effect of higher fluid intake was observed in studies including Asian patients.

For bladder cancer prevention, not only the amount of total water intake but also drinking water 'byproducts' which seem to be abundant [25] are important to study. There might be a carcinogenic role of cadmium, lead, chromium, calcium, potassium, phosphorous, magnesium, nickel, selenium, strontium and zinc as high concentrations of those elements can be found in radical cystectomy specimens of bladder cancer patients and significantly less frequently in healthy urothelium [26]. Inconsistent associations between bladder cancer risk and drinking water byproducts (e.g. nitrate content [27] and arsenic [28,29]) have been reported but those varying association can be explained by regional differences. Nevertheless, not only drinking water but also food may contain carcinogenic byproducts including nitrates [30], arsenic [29,31] and arylamines [32], which all have been linked to bladder cancer.

LIFESTYLE

The biggest contributor, in terms of lifestyle, toward the development and recurrence of bladder cancer is the use of tobacco and this is covered by a separate review in this issue.

Environment

It has been suggested that the byproducts of water disinfection such as chlorinated and brominated trihalomethanes (THMs) may increase the risk of bladder cancer. This risk was evaluated in a recent population-based case–control study from the National Cancer Institute in the United States [33]. This showed a weak association between drinking water with high levels of THMs and bladder cancer (OR 1.53, 95%CI: 1.01–2.32). A particular concern has been the widespread use of THMs for disinfecting swimming pool water. However, this study did not find any association between swimming pool use and bladder cancer.

Exposure to pesticides among agricultural populations has been associated with an increased risk of developing bladder cancer. Koutros *et al*. examined data from a prospective cohort study of

pesticide applicators and found an increased risk of bladder cancer associated with the specific pesticides Imazethapyr (rate ratio 1.54, 95% CI 1.05–2.26) and Imazaquin (rate ratio 3.03, 95% CI 1.46,6.29). Both these pesticides are aromatic amines. They also observed an increased risk with several chlorinated pesticides [34].

A recent study examining the relationship between sunlight and cancer found that increased sunlight exposure was associated with decreased incidence and mortality from bladder cancer. It was postulated that this may be because of the protective role of vitamin D in reducing cell proliferation and angiogenesis while increasing cell differentiation [35].

Lifestyle

A large number of lifestyle factors and their association with the risk of developing cancer have been reported, but few studies have looked specifically at the risk of developing bladder cancer. In a recent study of perceived stress at work and developing all cancers, a stressful job was weakly associated with an increased risk of developing bladder cancer among others (OR = 1.37, 95% CI: 1.03–1.81) [36]. Similarly, Chen *et al.* [37] have found a weak association between anxiety disorders and the development of bladder cancer (hazard ratio = 2.94, 95% CI: 1.89–4.58), whereas Gu *et al.* [38] found a weak association between less than 7–8 h sleep duration and bladder cancer (hazard ratio = 1.10, 95% CI: 1.00–1.20).

Conversely, a study of the role of exercise and smoking in bladder cancer mortality found that those who exercised were 47% less likely to die of bladder cancer than those who did not (hazard ratio 0.53, 95% CI 0.29–0.96). However, there was no association between BMI (and hence obesity) and bladder cancer mortality [39]. A Finnish study of women who had had at least five deliveries found a decreased incidence of bladder cancer (standardised incidence ratio 0.7, 95% CI: 0.61–0.78). The authors speculated that pregnancy-related changes in sex steroids may play an antioncogenic role in bladder tissue [40].

Recreational drug use

A recent meta-analysis examining the role of smoking opium on developing bladder cancer showed an increased risk for developing bladder cancer (OR 3.85, 95% CI: 3.05–4.87). Prolonged intake of opium was associated with an increased risk. It was postulated that this may be the result of exposure to mutagenic compounds such as opium pyrolysates, but many opium users also smoke tobacco which makes assessing the true risk of opium smoking difficult to assess [41].

CONCLUSION

In summary, many risk factors and some preventive interventions have been studied by several groups in different countries and ethnicities. Numerous food, fluid and life style frequency questionnaires have been used to study single food items, dietary scores, life style and environment and their association with bladder cancer. However, in most data sets, the limited bladder cancer incidence leads to an insufficient number of bladder cancer cases and insufficient power to test for modest risk factors. Furthermore, a high number of potential risk factors in large data sets cause problems of statistical validity and often result in spurious and sometimes contradictory but significant associations because of multiple testing. For many significant associated and so-called risk factors, there is no consistent or convincing evidence of a causal relation and often residual confounding or type 1 errors may be the most appropriate explanation.

The level of evidence of many published risk factors should be questioned because the limited number of interventional trials failed to confirm a protective effect of a certain change in diet against bladder cancer [3]. Although this may be disappointing for a physician trying to improve the fate of his patient, this may be comforting for patients who can be reassured that their diet and lifestyle did not cause their bladder cancer and that they do not have to change their current lifestyle and preferred diet. Nevertheless, we agree that although there is only spare evidence to promote a specific diet to prevent bladder cancer, there is evidence that a healthy life style should at least be encouraged to improve cardiovascular health [42].

We look forward to prospective trials with prespecified statistical analysis plans, appropriate control of confounders and innovative interventions as well as to properly conducted systematic reviews with appropriate search protocols and meta-analysis according to current guidelines. In this regard, the results of a multiinstitutional database are eagerly awaited [43▪].

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Conflicts of interest

There are no conflicts of interests.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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Impressive multicenter study protocol of outstanding interest.